Paper No. 29

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte FABRIZIO SAMARITANI and PATRIZIA NATALE

Appeal No. 2001-2399
Application No. 08/737,633

ON BRIEF

Before WILLIAM F. SMITH, LORIN and MILLS, Administrative Patent Judges.

LORIN, Administrative Patent Judge.

VACATUR AND REMAND TO EXAMINER

This is an appeal under 35 U.S.C. § 134 from the final rejection of claims 1, 3, 5-7, 9 and 10.[1]

[1] Pursuant to 35 U.S.C. § 6(b), we review the adverse decision of the examiner. In doing so, we have considered the record, including:

- Final Rejection (Paper No. 7);
- Advisory Action (Paper No. 10);
- Second Final Rejection (Paper No. 14);
- Brief (Paper No. 17);
- Rejection (Paper No 19);
- Third Final Rejection (Paper No. 22);
- Request for Reconsideration (Paper No. 25);
- Advisory Action (Paper No. 26); and,
- Examiner's Answer (Paper No. 28).

Claims 1, 9 and 10 are illustrative of the claims on appeal and read as follows:

1. A liquid pharmaceutical formulation consisting of from about 0.6 to 24 MIU/ml of interferon-beta, mannitol, a buffer at a pH between 3.0 and 4.0 and, optionally, albumin.

9. A process for the preparation of a pharmaceutical formulation according to claim 1, comprising combining interferon-beta with mannitol, a buffer at pH between 3.0 and 4.0 and, optionally albumin.

10. A container hermetically sealed in sterile conditions comprising the liquid pharmaceutical formulation according to claim 1 and appropriate for storage prior to use.

The references relied upon by the examiner are:

Cymbalista et al. (Cymbalista)	U.S. 4,647,454	March 3, 1987
Hershenson et al. (Hershenson)	U.S. 5,004,605	April 2, 1990
Hanisch et al. (Hanisch)	U.S. 5,643,566	July 1, 1997

The rejections are:

- Claims 1, 3, 7, 9 and 10 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Hanisch.

- Claim 5 stands rejected under 35 U.S.C. § 103(a) as being unpatentable over Hanisch as applied to claims 1, 3, 7, 9 and 10 above and further in view of Cymbalista.

- Claim 6 stands rejected under 35 U.S.C. § 103(a) as being unpatentable over Hanisch as applied to claims 1, 3, 7, 9 and 10 above and further in view of Hershenson.

DISCUSSION

In reviewing, on appeal, a PTO Board's findings and conclusions, the Federal Circuit has stated that "[f]or judicial review to be meaningfully achieved within these strictures[2], the agency tribunal must present a full and reasoned explanation of its decision. The agency tribunal must set forth its findings and the grounds thereof, as supported by the agency record, and explain its application of the law to the found facts." In re Lee, 277 F.3d 1338, 1342, 61 USPQ2d 1430, 1432-3 (Fed. Cir. 2002). "The agency tribunal must make findings of relevant facts, and present its reasoning in sufficient detail that the court may conduct meaningful review of the agency action." Ibid. at 277 F.3d 1346, 61 USPQ2d 1435. "Remand for these purposes is required." Ibid. at 277 F.3d 1346, 61 USPQ2d 1436."

Since the Board also serves as a board of review, not a de novo examination tribunal (35 U.S.C. § 6(b)), in order for the Board to make a meaningful review of the rejections on appeal, examiner likewise must present a full and reasoned explanation in support of the final rejection. As we explain

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[2] "5 U.S.C. §706(2) The reviewing court shall—
(2) hold unlawful and set aside agency actions, findings, and conclusions found to be—
(A) arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law;
* * * *
(E) unsupported by substantial evidence in a case subject to sections 556 and 557 of this title or otherwise reviewed on the record of an agency hearing provided by statute;"
In re Lee, 277 F.3d 1338, 1342, 61 USPQ2d 1430, 1433-4 (Fed. Cir. 2002).

below, that has not been done here. Accordingly, we remand the application to give the examiner a new opportunity to more thoroughly present the grounds of rejection. If the opportunity is taken, examiner should consider applying the Hershenson reference against all the claims. As we explain below, the combination of Hanisch and Hershenson would appear to raise a stronger question of patentability than the one presented here. Accordingly, we will vacate the present rejections and remand the application to give the examiner an opportunity to consider applying a new grounds of rejection.

The claims are directed to a formulation, a process of making a formulation and a container containing a formulation consisting of "from about 0.6 to 24 MIU/ml of interferon-beta, mannitol [and] a buffer at a pH between 3.0 and 4.0." The claims have been rejected as obvious under 35 U.S.C. § 103 over at least Hanisch. Accordingly, examiner has the burden of establishing a prima facie case of obviousness for a formulation consisting of "from about 0.6 to 24 MIU/ml of interferon-beta, mannitol [and] a buffer at a pH between 3.0 and 4.0" based on the disclosure in Hanisch. In re Oetiker, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992).

To meet the burden of establishing a prima facie case of obviousness of the claimed formulation over Hanisch, examiner (examiner's answer, p. 3) makes the following factual statements:

> Hanisch describes formulations for the stable storage of 'lipophilic proteins,' including the particularly exemplified IL-2 and INF-beta (Abstract). It teaches that a formulation having essentially only INF-beta, human serum albumin and a buffer (as is obtained following practice of the prescribed purification protocol) may be prepared at an acidic pH, preferably 3.5, and that under such conditions '[t]he beta-INF formulation will remain stable and soluble.' (Column 12, lines 53-65). It further teaches that the formulation 'can be maintained as a liquid with or without a carbohydrate stabilizer,' and that, following the optional addition of such stabilizer, the formulation may be lyophilized. Id. The patent teaches that a number of carbohydrate stabilizers, including mannitol, may be employed in the formulation it describes (column 9, lines 21-37). Hanisch does not exemplify a formulation consisting of INF-beta, HSA, a buffer and mannitol.

Examiner addresses all but one of the limitations for the claimed formulation. Absent from the stated facts is any mention of the claimed interferon-beta dosage quantity of from about 0.6 to 24 MIU/ml. All that is stated is that "[i]t ... would have been obvious to have dispensed the formulation in unit dosage quantities ... because Hanisch teaches that 'lyophilized formulation can then be reconstituted for clinical administration'... ." Examiner's Answer, p. 4. Nowhere in the grounds of the rejection is the dosage quantity addressed. No factual analysis has been presented explaining how one of ordinary skill reading Hanisch would be led to provide interferon-beta in the formulation at a dosage quantity of from about 0.6 to 24 MIU/ml. All that we have is examiner's conclusion that it would have been obvious to have dispensed the formulation in unit dosage quantities, a conclusion which, too, fails to account for the quantities claimed. Even if we presumed that examiner is arguing that an interferon-beta dosage quantity of from about 0.6 to 24 MIU/ml would have been obvious over Hanisch's broad disclosure of clinical administration of interferon-beta, we are

still not placed in a position to determine whether the facts support or do not support this position. Examiner provides no facts relating clinical administration to interferon-beta dosage quantities. The necessary information to connect the process of clinical administration and an interferon-beta dosage quantity that would fall within the claimed range has not been provided. Accordingly, we are not presented sufficient facts to make a meaningful review of examiner's position.

Examiner's conclusion of obviousness over the cited prior art combination must be supported by substantial evidence as supported by the record. See In re Lee, 277 F.3d 1338, 1343, 61 USPQ2d 1430, 1432 (Fed. Cir. 2002). The legal conclusion that there exists a prima facie case of obviousness is based on factual inquiries. See Graham v. John Deere Co., 383 U.S. 1, 17-18, 148 USPQ 459, 467 (1966). "The factual inquiry whether to combine references must be thorough and searching." McGinley v. Franklin Sports, Inc., 262 F.3d 1339, 1351-52, 60 USPQ2d 1001, 1008 (Fed. Cir. 2001).

> The patent examination process centers on prior art and the analysis thereof. When patentability turns on the question of obviousness, the search for and analysis of the prior art includes evidence relevant to the finding of whether there is a teaching, motivation, or suggestion to select and combine the references relied on as evidence of obviousness.

In re Lee, 277 F.3d 1338, 1342-1343, 61 USPQ2d 1430, 1434 (Fed. Cir. 2002).

We find that the factual support for examiner's position with respect to the claimed interferon-beta dosage quantity has not been thoroughly presented and therefore the conclusion of obviousness is not supported by substantial

evidence. Until we know examiner's reasoning leading up to the conclusion that the claimed dosage quantity for the interferon-beta component would have been obvious over Hanisch, the panel cannot make a meaningful review of the rejection of the claims. As a result, we remand the application for further clarification of the grounds of rejection.

In addition, we will vacate the rejections. In clarifying the grounds of rejection, examiner may want to consider including Hershenson as prior art against all the claims.

The characteristic feature common to the invention described in claims 1, 3, 5-7, 9 and 10 is a liquid pharmaceutical formulation consisting of

- From about 0.6 to 24 MIU/ml of interferon-beta,
- Mannitol,
- A buffer at a pH between 3.0 and 4.0 and,
- Optionally, albumin.

Examiner's position is that this formulation, as illustrated by sole independent claim 1 (see supra), would have been obvious over Hanisch. As we have already shown, examiner has not supported this position with substantial evidence. In fact, reading examiner's arguments, it would appear that examiner agrees with our view. In a discussion about the claimed interferon-beta dosage quantities, made in response (Examiner's Answer, pp. 6-7) to appellants' arguments (Brief, p. 2), examiner cites Hershenson for its disclosure of a range of known unit dosage levels, going so far as to conclude "[i]t would have been obvious to prepare a formulation of IFN-beta containing only half the amount

exemplified by Hanisch [see footnote 2, supra] ... because Hershenson et al. teach a range of unit dosages are employed in the art for pharmaceutical preparations of IFN-beta ... ." Examiner's Answer, p. 6. However, a rejection over Hanisch in view of Hershenson has not been made and therefore we are not presently in a position to decide the merits of such a rejection. Nevertheless, for the reasons to follow, Hershenson does appear to provide the necessary evidence, that is now lacking, to support examiner's position that the claimed interferon-beta dosage quantity would have been obvious to one of ordinary skill reading Hanisch.

Hanisch teaches a liquid[3] pharmaceutical formulation containing interferon-beta and mannitol[4] which remains "stable and soluble in a pH range of from ... between 3.0 and 4.0"[5]. Hanisch differs from the claimed invention in that it does not suggest a dosage quantity for the interferon-beta in the carbohydrate-stabilized formulation. Hanisch does not disclose any particular interferon-beta dosage quantity. However, because Hanisch intends to use a therapeutically effective amount of interferon-beta (col. 5, line 27) to be used as, for example, an

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[3] According to Hanisch (col. 12, lines 61-65), "The [β-HIFN formulation] **can be maintained as a liquid with or without a carbohydrate stabilizer**; or a carbohydrate stabilizer, preferably dextrose, can be added and the solution can be lyophilized. The lyophilized formulation can then be reconstituted for clinical administration."

[4] "Examples of such stabilizers include ... carbohydrates preferably chosen from ... **mannitol** ... ." Hanisch, col. 9, lines 31-37.

[5] "The β-HIFN formulation will remain stable and soluble in a pH range of from about 2 to about 4, preferably 3 to 4, and most preferably at about pH 3.5." Hanisch, col. 12, lines 58-61.

anitiviral agent (col. 2, line 34), the Hanisch formulation would suggest using any known dosage quantity of interferon-beta for that purpose.

Hershenson, which like Hanisch is directed to using therapeutically effective amounts of interferon-beta (col. 4, lines 42-43) in stabilized formulations, which interferon-beta is also intended to be used as, for example, an antiviral agent (col. 1, line 56), teaches that "the concentration of the stabilizer/solubilizers[6] of this invention varies with the concentration of IFN-β in the formulation." In particular,

> A high dosage formulation of IFN-β is that which contains about 1 to about 2 mg/ml of IFN-β in the final container vial (2 to 4 x 10^8 units per mg). A normal dosage formulation has about 0.25 mg/ml of IFN-β in the final container vial (0.5 x 10^8 units per mg); whereas, a low dosage formulation has about 0.125 mg/ml of IFN-β in the final container vial (0.25 x 10^8 units per mg).

This passage indicates that a "normal" dosage would contain 12.5 MIU/ml[7] of interferon-beta. That falls squarely within the claimed range of 0.6 to 24 MIU/ml.

Accordingly, given Hershenson's indication that a normal dosage of interferon-beta in a stabilized formulation would be 12.5 MIU/ml and that both Hanisch and Hershenson disclose interferon-beta stabilized formulations to be used for the same purpose, there is substantial evidence to conclude that one of

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[6] Hershenson is directed to a protein stabilizers such as albumin (see col. 3, line 29). By contrast, Hanisch is more broadly directed to carbohydrate and/or protein stabilizers.

[7] Hershenson indicates that a normal dosage is "0.25 mg/ml of IFN-β in the final container vial (0.5 x 10^8 units per mg)." Accordingly, a normal dosage is (0.25 x 50,000,000 IU)/ml, or 12,500,000 IU/ml (i.e., 12.5 MIU/ml). We note that examiner's argument (Examiner's Answer, bottom of p. 6) relies on Hershenson's low dosage disclosure. The disclosed low dosage ("0.125 mg/ml of IFN-β in the final container vial (0.25 x 10^8 units per mg)" calculates out to be 3.125 MIU/ml, which also falls within the claimed range.

ordinary skill making the Hanisch formulation to be used as, for example, an antiviral agent, would consider employing a "normal" dosage quantity of interferon-beta as Hershenson defines it. Since the combination of using Hershenson's "normal" dosage of interferon-beta in the Hanisch formulation would lead one to the claimed invention, a prima facie case of obviousness for the claimed invention over Hanisch in view of Hershenson would appear to be established.

For the foregoing reasons, upon further prosecution, examiner should consider raising a new rejection under 35 U.S.C. § 103 over Hanisch in view of Hershenson.

In raising a new rejection under 35 U.S.C. § 103 over Hanisch in view of Hershenson, we advise examiner to also include a thorough analysis of why the prior art combination would lead one of skill to modify the Hanisch formulation to use the buffer as described in claim 1. Presently, examiner (Examiner's Answer, p. 3) states that Hanisch teaches "a buffer (as is obtained following practice of the prescribed purification protocol)." However, there is no straightforward connection between a buffer used during a purification step and a buffer used as a component in an interferon-beta stabilized formulation. If, during subsequent prosecution, examiner should repeat this point, examiner should clarify how a buffer used during a purification step would necessarily make itself present in the resulting liquid formulation of stabilized interferon-beta.

With regard to claim 3, both Hanisch (col. 2) and Hershenson (col. 1) indicate that the stabilized formulation can contain recombinant interferon-beta.

With regard to claim 5, this claim is presently rejected over Hanisch in view of Cymbalista. For the reasons already stated and given that claim 5 depends on claim 1, examiner should consider including Hershenson among the prior art over which this claim is rejected.

With regard to claim 6, claim 6 depends on claim 4. Claim 6 has been rejected but claim 4 has been indicated as having allowable subject matter (see Final Rejection, paper no. 22, p. 3). It is not clear to us why examiner has rejected claim 6 as obvious under 35 U.S.C. § 103 over the cited prior art given that underlying claim 4 has not been given the same treatment. Examiner's position as to the patentability of claim 6 is at odds with the position examiner has taken, on this record, with respect to broader claim 4 on which it depends. These two claims should be given consistent treatment.

With regard to claim 7, both Hanisch (col. 9, line 32) and Hershenson (col. 3, line 29) indicate that albumin can be used to stabilize interferon-beta.

With regard to claim 9, which is directed to a process of making the formulation of claim 1, for the reasons already stated and given that claim 9 depends on claim 1, examiner should consider including Hershenson among the prior art over which this claim is rejected.

With regard to claim 10, which is directed to container including the formulation of claim 1, for the reasons already stated and given that claim 9

depends on claim 1, examiner should consider including Hershenson among the prior art over which this claim is rejected.

For the foregoing reasons, we vacate the rejections under § 103 and remand to give the examiner an opportunity to consider the issues discussed herein and take appropriate action not inconsistent with the views expressed herein. We emphasize that we vacate examiner's rejections. This means that the instant rejections no longer exist and the issues set forth herein cannot be satisfied by a Supplemental Examiner's Answer. See Ex parte Zambrano, 58 USPQ2d 1312, 1313 (Bd. Pat. App. & Int. 2000).

VACATED AND REMANDED

WILLIAM F. SMITH
Administrative Patent Judge

HUBERT C. LORIN
Administrative Patent Judge

DEMETRA J. MILLS
Administrative Patent Judge

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